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Botulinum toxin type A in scar treatment: Review article

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ABSTRACT

Introduction: Botulinum toxin type A (BoNTA) has become widely recognized for its expanding abilities of use in various medical fields. Recently, numerous studies and randomized clinical trials have proved its effectiveness in treating postoperative scars, hypertrophic scars, and keloids. This review analyzes clinical trials and scientific literature to assess the benefits of BoNTA injections in reducing scar visibility, enhancing healing, and improving skin appearance. The research also describes the mechanism of action, optimal treatment time, and the role of botulinum toxin in scar management. *Purpose:* This review aims to summarize the mechanism of action of botulinum toxin, its current clinical applications in scar management, and potential future directions for its therapeutic use. *Results:* Botulinum toxin promotes proper tissue healing and influences scar formation through anti-inflammatory effects, muscle relaxation, and collagen synthesis regulation. *Conclusions:* Botulinum toxin is an effective agent in scar treatment, as supported by randomized scientific studies. It has anti-inflammatory properties, reduces pain and itching, and enhances post-healing skin appearance.

Keywords: Botulinum toxin; scars; BoNTA; keloid; scar treatment.

1. INTRODUCTION

Botulinum toxin is one of the most harmful poisons, with its first appearance in reports dating back to the 17th century. Botulism cases documented in Western Germany by Justinus Kerner (1786-1862) were the first precisely described symptom complexes occurring after consumption of meat containing Clostridium botulinum strains. Potentially deadly cases of botulism were associated not only with food poisoning but also with wound contamination or colonization of the gastrointestinal tract in infants (Willis et al., 2008). This discovery became the beginning of botulinum toxin therapy, starting from its first application by Alan B. Scott in 1977 in strabismus treatment (Whitcup, 2021). Botulinum toxin type A (BoNTA) for medical usage was first approved by the FDA (Food and Drug

Administration) in 1989 in the United States and since has become permanently among the drugs very frequently used in medicine (Choudhury et al., 2021).

Its potential has been utilized in treating neurological-muscular conduction disorders such as strabismus, eyelid spasm, hemifacial spasm, spasticity or dystonia, as well as those not related to conduction disorders such as hyperhidrosis, migraines or urinary incontinence (Ababneh et al., 2014). In aesthetic medicine it is used with continually increasing interest in reducing mimic wrinkles and improving skin quality. There is also a regular increase in the number of indications for off-label use of BoNTA, including new cases such as bruxism or allergic rhinitis (Grando and Zachary, 2018). In recent years, many studies have also confirmed its positive impact on the remodeling of scar tissue, not only in the case of fresh scars but also mature ones (Prodromidou et al., 2015). Its main action on muscle tissue and other non-neuronal mechanisms of action are employed in scar treatment (Grando and Zachary, 2018).

2. METHODOLOGY

The review article was composed based on a review of 34 reports, studies, and books from medical databases such as PubMed, CrossRef, Google Scholar, and scientific books. The research lasted about 2 months, during which scientific articles and literature have been carefully selected from those available to the scientific community, based on their relevance, publication date, and the accuracy of the analyses conducted. The used keywords included “botulinum toxin”, “scar treatment”, “keloid treatment”, “hypertrophic scar treatment", “new methods of scar treatment", “botulinum toxin in aesthetic medicine”, “botulinum toxin in scar treatment”, “botulinum toxin guidelines”.

3. RESULTS AND DISCUSSION

Structure and Mechanism of Action

Botulinum toxin is an exotoxin with a mass of 150 kDa produced by Clostridium botulinum and has eight serotypes. In medicine, type A (BoNTA) is used most frequently, and rarely type B (BoNTB), primarily due to the longer duration of action and lower risk of adverse effects associated with the serotype A use (Dashtipour and Pedouim, 2016). The botulinum toxin molecule consists of two polypeptide chains: a heavy chain with a mass of 100 kDa and a light chain with a mass of 50 kDa, which are linked together by one disulfide bond (Figure 1). The neurotoxin complex also comprises three non-toxic hemagglutinin proteins (HA) and one non-toxic non-hemagglutinin protein (NHA), playing roles in transportation and complex protection (Kalb et al., 2017).

In the construction of complexes used in therapeutic and experimental medicine, proteinaceous excipients are built-in complex and they are primarily responsible for the specific properties of the drug, such as high efficacy, longer action duration and decreased risk of adverse effects (Comella et al., 2005). BoNTA inhibits acetylcholine release by directing blockade of the transmission of soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) transmembrane protein groups, restricting the fusion of synaptic vesicles with the inner surface of the axonal plasma membrane. The absence of the necessary mediator enabling the signal transimssion causes temporary cessation of muscle contraction activity, and blockade of secretion by exocrine glands. The blockade is relieved through the natural renewal process of the SNARE complex (Willis et al., 2008) (Figure 2, 3).

Wound Healing

A wound occurs due to a disruption in the integrity of the skin layer. The healing process is a complicated sequence of events that can be divided into several phases. These include the inflammatory, proliferation and remodeling phases. The inflammatory phase begins immediately after the injury and it is characterized by forming of a blood clot by platelets to stop bleeding and the influx of inflammatory cells such as neutrophils and monocytes. Damaged cells and external pathogens are removed via phagocytosis, and signaling through chemotaxis stimulates fibroblasts and endothelial cells, providing forming of granulation tissue, known as the proliferation phase. In the final phase – the remodeling phase – the excess of accumulated cells are eliminated in apoptosis process, with the involvement of metalloproteinases (MMPs) leading to a reduction in the amount of extracellular matrix, and collagen fibers undergo reorganization (Wilgus, 2007).

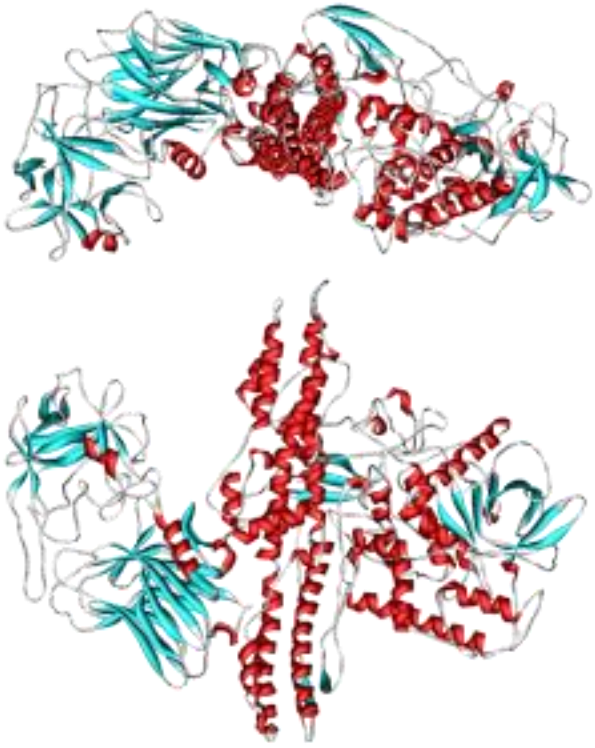

Figure 1 Ribbon model of botulinum toxin type A.

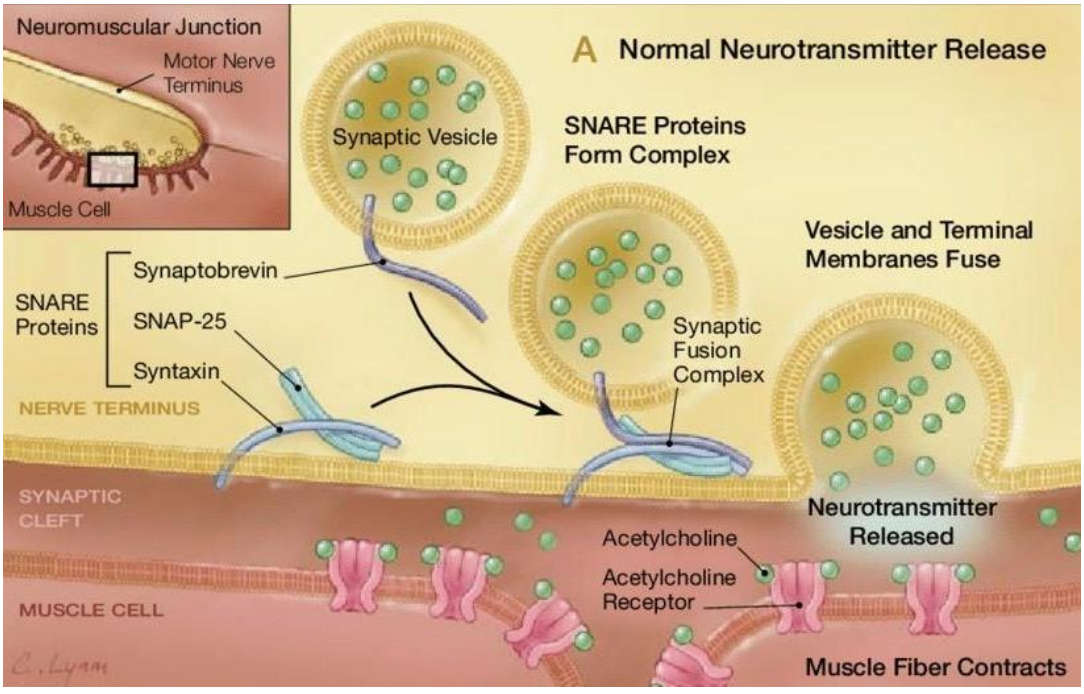

Figure 2 Physiological release of neurotransmitter at the neuromuscular junction.

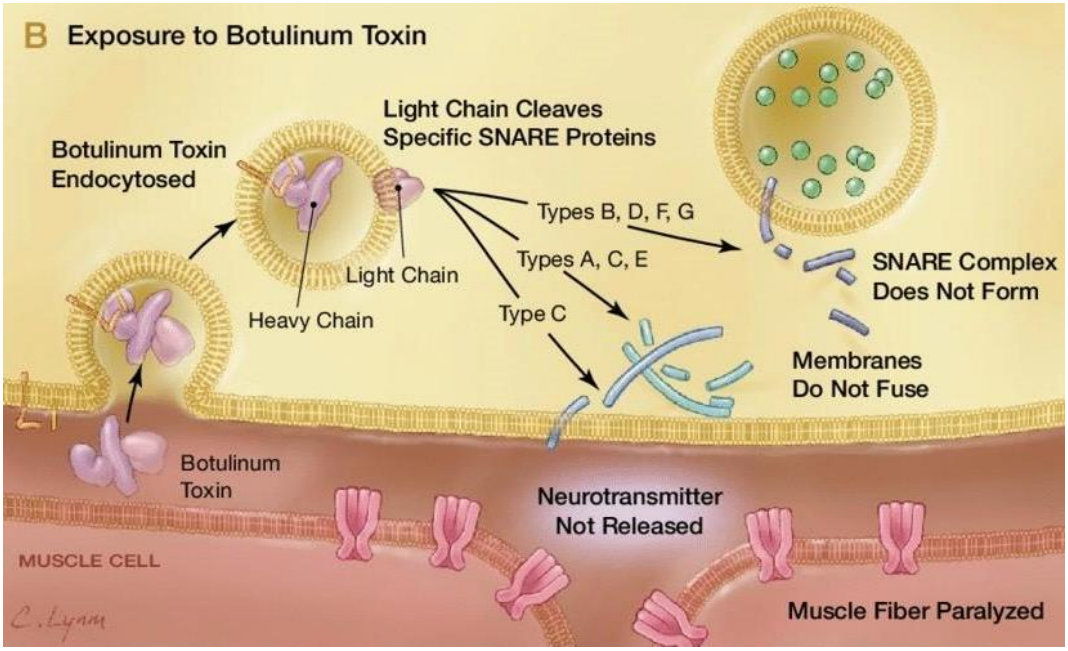

Figure 3 Function of the neuromuscular junction following the application of Botulinum Toxin Type A.

The Formation of Pathological Scars

Both hypertrophic scars and keloids are defined as scars characterized by prolonged and aberrant healing, yet they are two distinct pathological entities. Despite sharing common features such as prolonged inflammatory responses, heightened TGF-β production, fibroblast differentiation into myofibroblasts, and excessive extracellular matrix deposition, they represent distinct pathological entities with differences in their pathogenesis and final appearance (Sarrazy et al., 2011). Keloids, also known as keloid scars, present a distinctive pathological pattern characterized by their proliferation beyond the natural margins of the primary wound.

Histologically, they are composed of thick eosinophilic collagen fibers forming nodules, featuring densely packed collagen fibers with an organized, although different compaction from the typical skin structure. In contrast, hypertrophic scars develop within the confines of the original wound borders and they are histologically characterized by the formation of raised skin structures without the distinct collagen fiber pattern observed in keloids. It is noteworthy that keloids, in comparison to hypertrophic scars, are relatively rare in clinical practice (Teot et al., 2020; Berman et al., 2017).

The Neuronal Mechanisms of Botulinum Toxin Action

The tension of the tissue forming the wound is one of the main factors determining its proper healing and ensuring the aesthetic appearance of the skin after completing the remodeling phase. Numerous scientific studies have confirmed that the temporary weakening of muscles in the immediate vicinity of the scar positively influences healing, accelerates its process, and guarantees a better scar appearance. It prevents separation of the wound edges, allowing for a reduction in skin tension.

The duration of Botulinum toxin action in muscles, depending on the patient's lifestyle, health and environmental factors, ranges from 2 to 4 months. Despite its shorter duration of action compared to the total time required to complete the healing process and potential need of repeating the procedure, Botulinum toxin ideally fulfills its role in the early stages when reducing skin tension and preserving tissue integrity is most crucial (Teot et al., 2020) (Figure 4, 5).

Figure 4 Hypertrophic post-traumatic scar, impeding patient's unrestricted articulation.

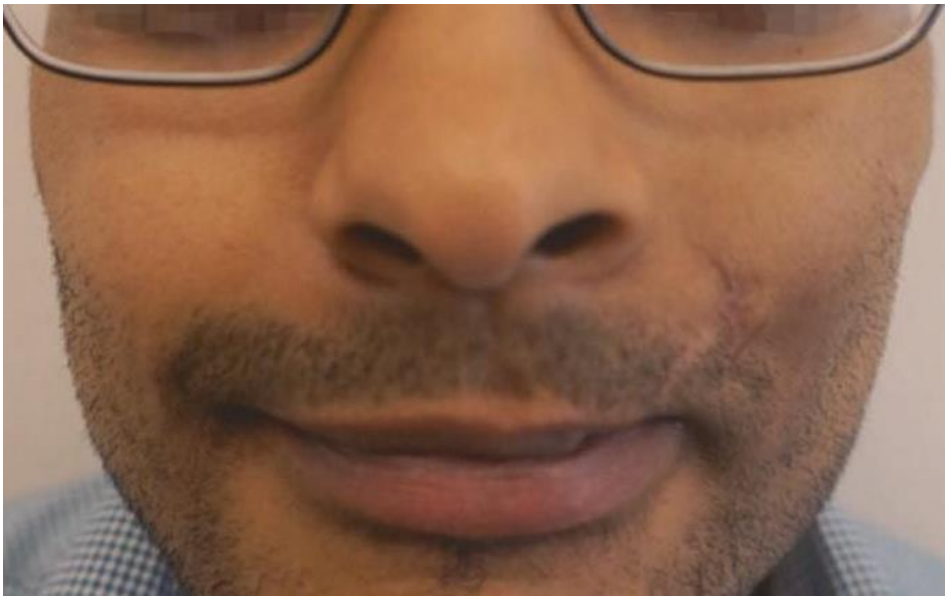

Figure 5 Scar with reduced dimensions and increased softness after a single application of Botulinum toxin.

One of the studies conducted by Lee et al., (2009) investigated the healing process of damaged skin on the rats backs. Each rodent underwent surgical excision of two round-shape wounds on the skin at a small distance from each other, making each animal at the same time a control for the other. In the experimental group, Botulinum toxin was applied to the muscles directly adjacent to the wound, while the control group received a saline injection around the wound area. The study revealed a significant difference in the appearance of the scar treated with Botulinum toxin compared to the control group. The BoNTA-treated scar had slightly larger dimensions, was less visible, and was flatter. The same study also demonstrated a reduced inflammatory response in the wounds from the experimental group (Lee et al., 2009).

Ziade et al., (2013) investigated the differences in scar appearance one year after skin injury by comparing 24 patients, among whom 11 individuals received 20IU of Botox® (ALLERGAN, Westport, Ireland) around the wound within 72 hours of injury. In 13 individuals, the wound edges were sutured without additional interventions. The overall assessment on the VAS scale after one year of observation was significantly more favorable in the case of Botulinum toxin use (Ziade et al., 2013). In another study, the use of

Botulinum toxin type A to using corticosteroids in the treatment of hypertrophic scars and keloids was compared. Comparative analysis demonstrated a better treatment efficacy of BoNTA for scars compared to corticosteroids and placebo (Bi et al., 2019).

Non-neuronal mechanisms of Botulinum toxin action

Despite its action on the neurotransmission, effects of Botulinum toxin are not limited exclusively to the neuromuscular system. Besides its documented effects in this area, BoNTA also impacts on a range of other mechanisms of action on various cell types, as evidenced by numerous scientific studies. Cells that express the ability to produce Botulinum toxin binding proteins, receptors for BoNTA, or the SNAP-25 complex include epidermal keratinocytes, mesenchymal stem cells of subcutaneous adipose tissue, nasal mucosa cells, urothelial cells, intestinal epithelial cells, alveolar epithelial cells, macrophages, and neutrophils. Research has shown that BoNTA affects gene expression in each cell differently and exhibits a distinct profile of action in each case (Grando and Zachary, 2018).

Results from in vivo and in vitro experiments demonstrate multiple mechanisms of action of BoNTA on both neuronal and non-neuronal cells in the skin, explaining the benefits of its application in non-traditional dermatological or aesthetic medicine indications. Among these are hypertrophic scars, keloids, and slow-healing wounds. Accelerated wound healing or reduced scar thickness is observed, suggesting the use of BoNTA in treating the postoperative, post-burn, or post-traumatic scars. Botulinum toxin demonstrates variety of actions, including regulation of inflammatory response, influence on fibroblasts, regulation of TGF-β levels, collagen, and metalloproteinases (Teot et al., 2020). As a result, it is possible to alleviate troublesome symptoms such as stiffness, hardening, or pain, which are characteristic for scars of this type.

Reduction in scar thickness was documented in a study conducted by (Xiao and Qu, 2012). They demonstrated a significant decrease in scar thickness on rabbit ears, providing evidence through hematoxylin and eosin-stained sample observation, which clearly showed a difference in the thickness of scar tissue. The scar injected with Botulinum toxin appeared paler, more discreet, and flatter (Xiao and Qu, 2012). In scar treatment the aspect of regulation of the inflammatory response by BoNTA is essential. This response can be stimulated or inhibited, depending on whether the administered Botulinum toxin is bound to complexing proteins. In a study conducted by Wang et al., (2014) it was demonstrated that in the case of Xeomin® (Merz Pharmaceuticals, Germany), which is free from complexing proteins, BoNTA does not induce inflammation.

On the other hand, Botox® (ALLERGAN, Westport, Ireland), which contains Neurotoxin Associated Proteins (NAPs), exhibits anti-inflammatory effects (Wang et al., 2014). In other publications, it was demonstrated that BoNTA reduces the levels of COX-2, lymphocyte accumulation, and expression of cytokines, monocytes, and macrophages, providing the proper cycle of epidermal regeneration (Grando and Zachary, 2018; Lee et al., 2009; Chuang et al., 2009). BoNTA, as a medication that inhibits mast cells activity, is also used for anti-itch purposes. Currently, it is employed in some dermatological conditions associated with itching, such as psoriasis or lichen planus, and in the future, treatment of systemic conditions is not excluded (Cao et al., 2017; Gazerani, 2022).

It has been proven that BoNTA affects the expression of vascular endothelial growth factor (VEGF), platelet endothelial cell adhesion molecule-1 (PECAM-1), and tumor necrosis factor α (TNF-α), contributing to the formation of new blood vessels, improved blood flow, and faster healing. It possesses properties that prevent hypoxia and eliminate detrimental reactive oxygen species (Park et al., 2016). Botulinum toxin type A directly influences the formation process of scar tissue through its documented effects on fibroblasts, which, despite numerous studies conducted, cannot be unambiguously determined. In one of the studies, it was demonstrated that Botulinum toxin inhibits the formation of new fibroblasts and leads to a decrease in the amount of cellular connective tissue growth factor (CTGF) - a regulator of TGF-β function responsible for fibrosis (Xiao et al., 2011).

In a study examinating human fibroblasts, BoNTA inhibited the production of type I and III collagen but had a positive effect on the production of matrix metalloproteinases (MMPs), including MMP-2 and MMP-9. Similarly, in the study previously described by Xiao and Qu, (2012) unequivocal evidence of reduced collagen levels in treated rats was obtained (Lee et al., 2009). MMPs participate, among others, in the degradation of collagen fibers, which significantly contributes to the treatment of hypertrophic scars and keloids. Another study examining the effect of BoNTA on human fibroblasts precisely demonstrated its opposite action, documenting an increase in type I collagen synthesis and a decrease in MMP production (Oh et al., 2012). In this regard, more research and providing reliable scientific evidence is definitely necessary.

Treating pathologically overgrown, mature wounds such as keloids and hypertrophic scars is an extremely challenging task. In one of the scientific studies, it was demonstrated that in the treatment of keloids, botulinum toxin inhibits cell proliferation into myofibroblasts by inhibiting TGF-1β (Lee et al., 2016). In one study on keloid treatment, the authors decided to use a technique called

"microbotox", which involves a large number of shallow intradermal or subcutaneous injections to impact on muscle tissue as well as exocrine glands. In this study, benefits from performing Botulinum toxin procedures were also observed (Wu, 2011).

Treatment with Botulinum Toxin

The most significant factor ensuring the success of botulinum toxin therapy is the time elapsed from the wound appearing to the first BoNTA treatment. Scar formation can take up to 12 months, forming scars within a year of tissue damage, which are defined as immature scars. The optimal time for administering BoNTA appears undefined. In some studies, injection before surgery for preventive purposes is recommended (Lebeda et al., 2012). In subsequent studies, BoNTA was administered during surgery or within one day afterward (Lee et al., 2009; Flynn, 2009). There are also reports of injecting botulinum toxin within 72 hours of the procedure or during suture removal (Ziade et al., 2013; Goodman, 2010). There are many treatment strategies, but due to the non-neuronal mechanisms of action of BoNTA, the earlier the drug is administered, the better are the patient's chances for positive effects (Grando and Zachary, 2018).

Dosage appears to be an individual matter. One study compared the effects of botulinum toxin treatment on several-centimeter wounds in a 6-month follow-up. The scar formed after surgery was divided into two parts for therapeutic purposes. One half was injected with 4 U of BoNTA, and the other with 8 U. In this case, administering a doubled dose and weakening the muscles to a greater extent yielded significantly better results (Jablonka et al., 2012). However, it is a fact that in conducted studies, authors rarely decide to administer a dose greater than 10 U for minor wounds, such as those in the facial area. In a study conducted by Goodman, a dose of 5 U was administered (Goodman, 2010). In another study, a dose of 10 U was used. Chambers A recommends a dose of 15 - 20 U of BoNTA as sufficient for a scar from a surgical facelift measuring 15 - 20 cm (Teot et al., 2020). It should be noted, of course, that more extensive scars or mature keloids require higher doses of BoNTA (Table 1).

Table 1 Recent findings on the use of botulinum toxin in wound treatment.

Authors	Year	Study Focus	Key Findings
Grando and Zachary	2018	Non-neuronal and non-muscular effects of botulinum toxin	Botulinum toxin has potential applications in skin conditions, including scars and hyperhidrosis.
Prodromidou et al.,	2015	Botulinum toxin for wound scar prevention and healing	Botulinum toxin A improves scar appearance and reduces hypertrophic scar formation, especially when administered early.
Teot et al.,	2020	Management and emerging technologies in scar treatment	Integration of botulinum toxin into scar treatment protocols enhances outcomes, reducing scar formation.
Kalb et al.,	2017	Hemagglutinin negative botulinum progenitor toxins	Characterizes botulinum progenitor toxins lacking hemagglutinin, which may have unique therapeutic potentials.
Wilgus	2007	Regenerative healing in fetal skin	Explores how fetal skin heals without scarring and the implications for wound healing therapies.
Sarrazy et al.,	2011	Mechanisms of pathological scarring	Discusses the role of myofibroblasts in scarring and advances in targeting these cells to prevent pathological scars.
Berman et al.,	2017	Keloids and hypertrophic scars	Reviews pathophysiology and treatment options for keloids and hypertrophic scars, highlighting botulinum toxin's role.
Lee et al.,	2009	Effect of botulinum toxin on a rat	Demonstrates that botulinum toxin type A

		surgical wound model	reduces scar formation and enhances wound healing in a rat model.
Bi et al.,	2019	Botulinum toxin vs corticosteroid for hypertrophic scars	Botulinum toxin type A is as effective as corticosteroids for treating hypertrophic scars, with fewer side effects.
Xiao and Qu	2012	Botulinum toxin's effect on collagen in hypertrophic scars	Botulinum toxin type A reduces collagen deposition, thereby improving the appearance of hypertrophic scars.
Wang et al.,	2014	Botulinum toxin complex proteins and host response	Botulinum neurotoxin complex proteins modulate host cellular responses, which may influence therapeutic outcomes.
Cao et al.,	2017	Botulinum toxin's long-term anti-itch effect	Botulinum neurotoxin A reduces itch by downregulating TRPV1 and TRPA1 in the dorsal root ganglia of mice.
Gazerani	2022	Mechanisms of botulinum toxin in inhibiting itch	Reviews the molecular mechanisms through which botulinum toxin alleviates itch, focusing on neurotransmitter modulation.
Park et al.,	2016	Botulinum toxin and angiogenesis in surgical flaps	Botulinum toxin A enhances angiogenesis in surgical flaps by upregulating HIF-1α and VEGF, improving flap survival.
Xiao et al.,	2011	Botulinum toxin on connective tissue growth factor in scars	Botulinum toxin type A inhibits connective tissue growth factor, which could reduce fibrosis in hypertrophic scars.
Kim et al.,	2016	Botulinum toxin's effect on TGF-β/Smad signaling	Botulinum toxin type A disrupts TGF-β/Smad signaling, potentially reducing capsule formation around implants.
Oh et al.,	2012	Effect of botulinum toxin on dermal fibroblasts	Botulinum toxin type A inhibits fibroblast activity in vitro, which may reduce scarring and improve skin texture.
Lee et al.,	2016	Botulinum toxin and capsule formation around implants	Demonstrates that botulinum toxin type A reduces capsule formation around silicone implants both in vivo and in vitro.
Wu	2011	Skin resurfacing with Microbotox and keloid treatment	Microbotox is effective in treating keloids and improving skin texture, offering a minimally invasive option.
Lebeda et al.,	2012	Botulinum toxin in wound healing	Explores kinetic and reaction pathways of botulinum toxin in promoting wound healing, highlighting its efficacy.
Flynn	2009	Intraoperative botulinum toxin in facial reconstruction	Intraoperative botulinum toxin reduces postoperative scar formation and improves aesthetic outcomes in facial reconstruction.
Goodman	2010	Botulinum toxin in post-acne and traumatic scarring	Botulinum toxin is effective as a primary or adjunctive treatment for post-acne and

			traumatic scarring.
Chen et al.,	2021	Botulinum toxin dose effect on surgical scar appearance	Higher doses of botulinum toxin A significantly improve the appearance of surgical scars.
Jablonka et al.,	2012	Botulinum toxin to minimize facial scarring	Botulinum toxin minimizes facial scarring by reducing muscle movement and tension during wound healing.

4. CONCLUSIONS

Botulinum toxin has been used in medicine for many years, during which the number of indications for its use has significantly increased. Scientific research confirms its impact on amplifying the remodeling of scar tissue, which is not limited exclusively to its action on adjoining muscles but also involves various other mechanisms. BoNTA exhibits anti-inflammatory, anti-itch, muscle-relaxing properties, and reduces the synthesis of new collagen in hypertrophic scars. Although not all aspects of its action are fully understood, it represents a very promising element in scar therapy for the future.

Author's Contribution

Conceptualization: A Baranowska; Methodology: N Zalewska; Software: J Kawka; Check: A Baranowska; Formal Analysis Investigation: A Baranowska, K Filipek, N Zalewska, F Czyżewski, W Mrugała, S Mrugała, B Skierkowski, M Muciek, K Baranowska; Resources: A Baranowska, K Filipek, N Zalewska, F Czyżewski, W Mrugała, S Mrugała, B Skierkowski, M Muciek, K Baranowska; Writing – Rough Preparation: A Baranowska, K Baranowska, N Zalewska, K Filipek; Writing – Review and Editing: A Baranowska; Visualization: A Baranowska, J Kawka, F Czyżewski, M Muciek; Supervision: B Skierkowski, W Mrugała, S Mrugała, M Muciek; Project Administrator: A Baranowska. All authors have approved the submission of the manuscript.

Informed Consent

Not Applicable.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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